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ARTICLE

Effects of ATX-MS-1467 immunotherapy over 16 weeks in relapsing multiple sclerosis

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Abstract

Objective

To assess safety, tolerability, and efficacy of the antigen-specific immunotherapy ATX-MS-1467 in participants with relapsing multiple sclerosis using different treatment protocols to induce tolerance.

Methods

Two open-label trials in adult participants with relapsing multiple sclerosis were conducted. Study 1 was a multicenter, phase 1b safety evaluation comparing intradermal (i.d.) (cohort 1) with subcutaneous (cohort 2) administration in 43 participants. Both cohorts received ATX-MS-1467 dosed at 25, 50, 100, 400, and 800 μg at 14-day intervals over 8 weeks, followed by 8 weeks with 4 additional 800-μg doses at 14-day intervals and 32 weeks off study medication. Study 2 was a phase 2a, multicenter, single-arm trial enrolling 37 participants. ATX-MS-1467 was titrated from 50 μg i.d. on day 1 to 200 μg on day 15 and 800 μg on day 29 followed by biweekly administration of 800 μg for 16 weeks and 16 weeks off study medication. Efficacy was evaluated on MRI parameters and clinical variables. Safety endpoints included treatment-emergent adverse events and injection-site reactions.

Results

In study 1, there was a significant decrease in new/persisting T1 gadolinium-enhanced (GdE) lesions in cohort 1 from baseline to week 16, returning to baseline values at week 48. In study 2, the number of T1 GdE lesions were significantly reduced on treatment and remained reduced at study completion. Safety results were unremarkable in both studies.

Conclusion

Relatively slow ATX-MS-1467 titration and a longer full-dose i.d. treatment period is associated with reduction in GdE lesions and a sustained effect post treatment. Further trials of ATX-MS-1467 are warranted.

Classification of evidence

This work provides Class IV evidence that for patients with relapsing multiple sclerosis, slow ATX-MS-1467 titration and a longer full-dose i.d. treatment period is associated with reduction in GdE lesions.

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ATX-MS1467 Study Group coinvestigators are listed at links.lww.com/WNL/A233.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AE = adverse event; **ARR** = annualized relapse rate; **EDSS** = Expanded Disability Status Scale; **GdE** = gadolinium-enhanced; **i.d.** = intradermal; **ITT** = intention-to-treat; **MBP** = myelin basic protein; **mITT** = modified intention-to-treat; **MS** = multiple sclerosis; **MSFC** = Multiple Sclerosis Functional Composite; **RMS** = relapsing multiple sclerosis; **s.c.** = subcutaneous; **TEAE** = treatment-emergent adverse event.

By aiming to reinstate tolerance to the protein causing the disease,[1] antigen-specific immunotherapy represents a major conceptual shift away from most current and emerging immunomodulatory therapies for multiple sclerosis (MS).[2–7]

Peripheral tolerance is mediated by steady-state dendritic cells when peptides bind to major histocompatibility complex class II molecules at their surface, promoting interaction with antigen-specific T cells and subsequent generation of regulatory $CD4^+$ T cells.[8] The risk of an immune response can be avoided during tolerance induction by the use of synthetic peptides that mimic naturally processed $CD4^+$ T cell epitopes.[9,10] Such peptides have been termed apitopes, short for antigen-processing independent epitopes.[11]

We have identified epitopes from 4 regions of myelin basic protein (MBP) that behave as apitopes but also induce tolerance to myelin and reduce disease severity by up to 95% in a humanized mouse model when administered subcutaneously (s.c.) as a cocktail (ATX-MS-1467).[11] In an initial phase 1 trial of 6 participants with secondary progressive MS, ATX-MS-1467 was well tolerated, and there were significant immunologic changes consistent with a clinical effect on T cell responses to MBP 1 month after treatment compared to visit 1.[11]

The most appropriate ATX-MS-1467 titration scheme still needs to be identified. Accordingly, we performed 2 follow-up studies in participants with relapsing MS (RMS): one phase 1b ascending-dose safety evaluation comparing intradermal (i.d.) with s.c. administration and one proof-of-concept phase 2a trial assessing the effects on MRI parameters of ATX-MS-1467 administered i.d. and using a shorter dose-escalation phase with a prolonged highest-dose period.

Methods

Primary research questions

The aim of the 2 studies was to assess safety, tolerability, and efficacy of ATX-MS-1467 in RMS using different treatment protocols to induce tolerance.

Standard protocol approvals, registrations, and patient consents

Both studies were entered into public registries: the phase 1b study in the European Clinical Trials Database (number 2009-016710-25) and the phase 2a study on the ClinicalTrials.gov registry (identifier: NCT01973491). The studies were conducted in accordance with all applicable regulations, including the International Conference on Harmonisation Good Clinical Practice Guidelines and the ethical principles in the Declaration of Helsinki,[12] as well as local regulations and standards. The appropriate institutional review boards or regional review boards approved the use of human subjects for the studies. All participants gave written informed consent.

Participants

The studies were open-label trials in adult participants aged 18 to 55 years (study 1) and 18 to 65 years (study 2), respectively, with RMS (≥1 documented relapse in the previous 12 months or 2 relapses within the previous 24 months), as defined by the McDonald 2010 criteria,[13] positive for human lymphocyte antigen (HLA)-DRB1*15, and with Expanded Disability Status Scale (EDSS) scores ≤5.5. Prior and concomitant disease-modifying therapies were prohibited, except for interferon beta where adequate washout was required prior to study entry. Corticosteroids were permitted to treat relapses.

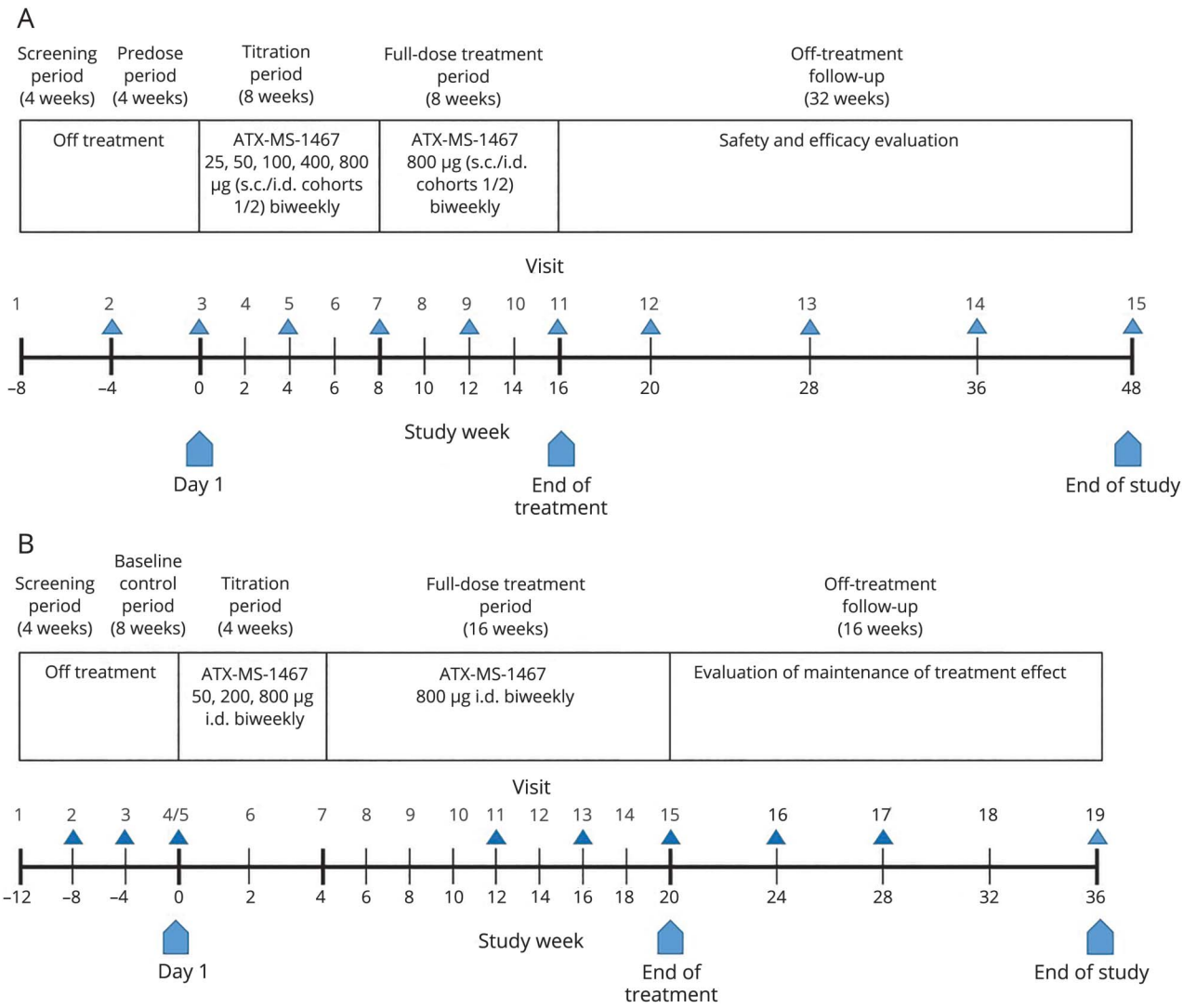
Phase 1b study (study 1)

The phase 1b study was a multicenter, 2-arm, ascending-dose safety and proof-of-principle study with the primary objective to assess the safety of ATX-MS-1467. Secondary objectives were to assess, on an exploratory level, the effect of ATX-MS-1467 on brain MRI (gadolinium-enhanced [GdE], 1.5-tesla MRI scanning).

The study enrolled 43 participants at 9 centers in the Russian Federation and 2 centers in the United Kingdom. Participants were divided into 2 cohorts. ATX-MS-1467 was administered i.d. in cohort 1 and s.c. in cohort 2. Participants were allocated to a cohort consecutively in the order of enrollment into the study. Dosing, titration, and intervals (figure 1A) were based on the earlier phase 1 study.[11] Over an 8-week titration period, both cohorts received increasing doses of ATX-MS-1467 of 25, 50, 100, 400, and 800 μg at 14 ± 3 day intervals. The titration period was followed by an 8-week, full-dose period during which participants received 4 additional 800-μg doses at 14 ± 3 day intervals. Participants were then followed for an additional 32 weeks off study medication.

Safety was assessed by the incidence of adverse events (AEs) and treatment-emergent AEs (TEAEs), examination of safety laboratory values, anti-peptide antibody tests, urine pregnancy tests, vital signs, physical examination, neurologic examination, and MRI evaluation of brain lesions. A TEAE was

Figure 1 Designs of the 2 studies



Time course, titration schemes, and assessment points are shown for the 2 studies. (A) Study 1 (phase 1b study); (B) study 2 (phase 2a study). Triangles indicate MRI measurements. i.d. = intradermal; s.c. = subcutaneous.

defined as an AE occurring on or after the first administration of ATX-MS-1467 and no later than week 20. A data monitoring committee reviewed the combined safety data for cohort 1 after the last dose of 800 µg was administered to the first 10 and 20 participants, respectively. The primary safety endpoints were evaluated on an ongoing basis up to week 20 and again at week 48. Safety was analyzed in the intention-to-treat (ITT) population, defined as all participants who received ≥1 administration of ATX-MS-1467 any time during the study.

Efficacy was assessed based on MRI evaluation of brain lesions as part of the safety evaluation on a proof-of-principle basis. Analyses included the presence of new T1 GdE lesions, new or enlarged T2 hyperintense lesions, and T1 hypointense lesions. The analyses were performed on the MRI population, defined as the per-protocol population (all ITT participants who complied with the protocol up to and including the week-20 visit).

In this explorative study, no formal sample size calculation was performed, and p values are presented for descriptive purposes only.

In both studies, continuous variables are summarized descriptively using the number of observations, means ± SD, 95% confidence interval, median, minimum, and maximum. Categorical variables are summarized using frequency counts and percentages.

Phase 2a study (study 2)

The phase 2a study was a multicenter, single-arm, proof-of-concept trial at 7 sites in the Russian Federation and 1 site in Latvia. The primary objective was to evaluate the effects of

ATX-MS-1467 administered i.d. compared with a baseline control period off treatment. Safety evaluation was a secondary objective.

The dosing, escalation, and intervals differed from the phase 1 studies in that a shorter titration regimen was used, followed by a longer highest-dose treatment period (figure 1B). During a 4-week titration period, the dose of ATX-MS-1467 was titrated from 50 μg on day 1 to 200 μg on day 15 and 800 μg on day 29. Subsequently, participants received biweekly administration of 800 μg ATX-MS-1467 for 16 weeks. Participants were then followed for an additional 16 weeks off study medication.

Efficacy was evaluated on MRI parameters and clinical variables. The primary endpoint was change in the number of T1 GdE lesions at the last 3 on-treatment scans compared with the number of T1 GdE lesions at the 3 baseline scans. Secondary endpoints included number and change from baseline in T1 GdE lesions at each visit post baseline, the number of new or newly enlarging T2 lesions post baseline, mean annualized relapse rate (ARR) at week 20, time to first relapse, and change from baseline in total EDSS scores and in total Multiple Sclerosis Functional Composite (MSFC) scores, both assessed at week 20. Relapses were objectively assessed by the investigator.

Safety endpoints included TEAEs, injection-site reactions, vital signs, clinical laboratory variables, ECGs, and the frequency and timing of premature study termination. A TEAE was defined as any AE occurring on or after the first dose and within 28 days after the date of last dose.

The sample size calculation assumed a 70% reduction in GdE lesions with treatment compared with baseline, with 5 ± 6 GdE lesions on average at baseline and 1.5 ± 1.8 GdE lesions on average during the posttreatment period.[14] Using a 2-sided 5% level, >80% and >90% power was reached with sample sizes of 12 and 14 participants, respectively. Thus, a sample size of 15 participants was selected.

Primary and secondary endpoints were analyzed in the modified ITT (mITT) population, which included all enrolled participants who received ≥1 dose of ATX-MS-1467 and had ≥2 MRI scans during the baseline control period and ≥2 MRI scans during planned on-treatment visits. Maintenance of response was analyzed in the "responders" population (participants in whom there was a ≥60% reduction from baseline in the number of T1 GdE lesions at week 20), and safety analyses were based on the safety population.

The primary endpoint was analyzed using a nonparametric Wilcoxon signed rank test. A supportive analysis was performed to estimate mean percentage reduction from baseline in new T1 GdE lesions using a generalized estimating equations linear regression model with negative binomial and Poisson link functions. Descriptive statistics were used for secondary endpoints at each applicable visit for the mITT analysis set. Time to event variables are presented as Kaplan-Meier estimates, median survival, and 95% confidence interval.

Results

Study populations

Flow diagrams for the 2 studies are shown in figure 2. In study 1, the ITT population consisted of 43 participants, the per-protocol population of 35, and the MRI population of 37 participants. A total of 42 participants completed the treatment phase of the study: 20 in cohort 1 and 22 in cohort 2. Nineteen participants in cohort 1 and 20 participants in cohort 2 completed the follow-up period; 2 participants discontinued and 1 was lost to follow-up. One participant attended all follow-up visits but did not receive the last dose of ATX-MS-1467 because of concerns of an allergic reaction and was not included in the follow-up analysis population.

In study 2, 37 participants were enrolled, of whom 19 completed the titration period and were included in the ITT, mITT, and safety populations. One participant discontinued before the end of the treatment period (because of diarrhea, recorded as an AE) and one participant withdrew consent after completing the treatment period. Seven participants demonstrated a ≥60% reduction from baseline in the number of T1 GdE lesions at week 20 and were included in the responder population.

Demographic characteristics at baseline are shown in the table. In both studies, all participants were Caucasian with mean ages approximately 30 years and 70% female. EDSS scores and number of MS relapses in the last 24 months were similar in both studies. The study 1 population had fewer GdE lesions at baseline (2.8 ± 6.80) than the study 2 population (7.4 ± 7.62).

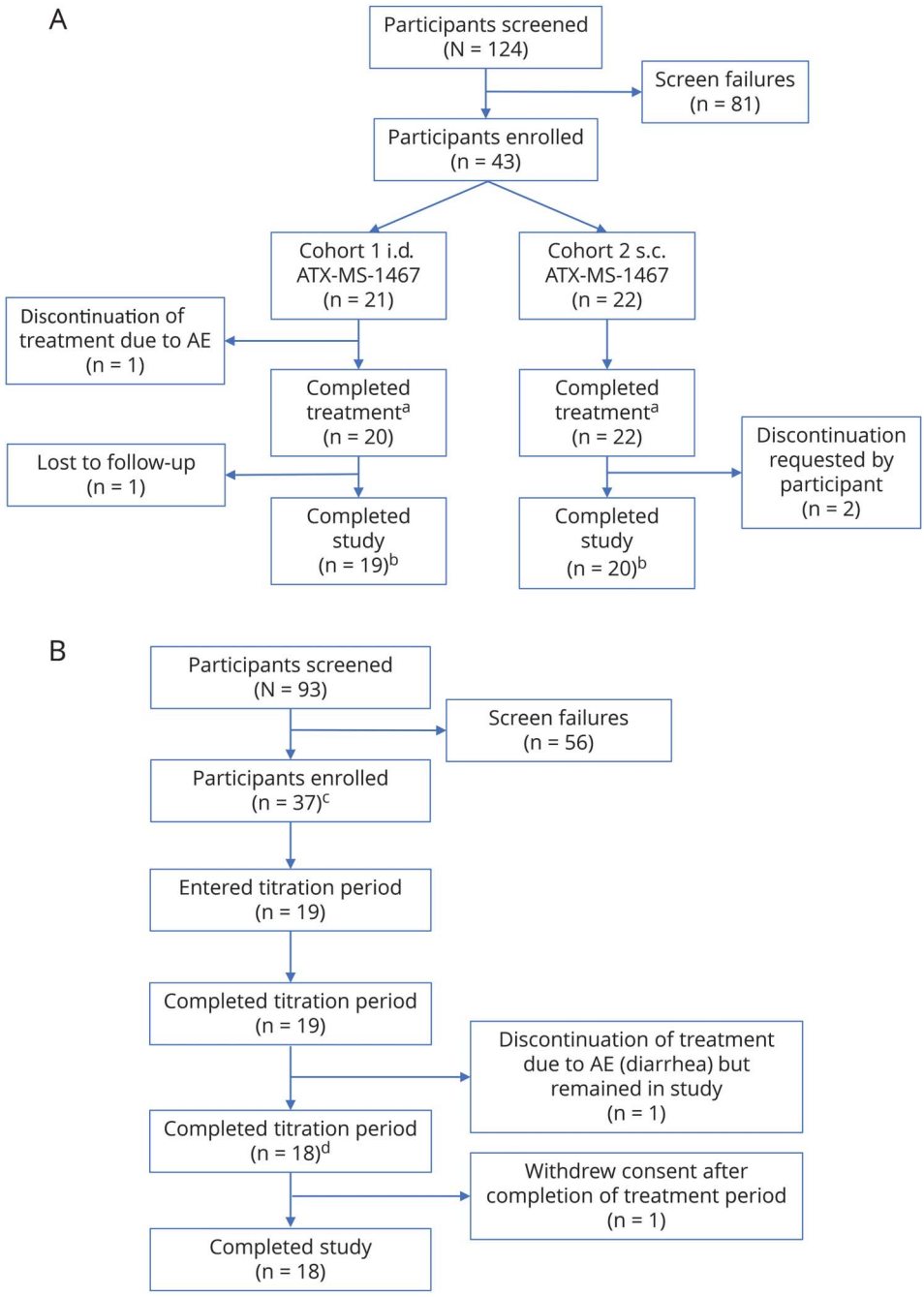
Efficacy results

In study 1, there was a significant 73% decrease in the number of new or persisting GdE lesions in cohort 1 from 3.4 ± 8.23 at baseline (week 0) to 0.9 ± 1.67 at week 16 (p = 0.030; figure 3A). The number of new or persisting lesions had returned to baseline values by study end. In cohort 2, the mean number of new or persisting GdE lesions was relatively low throughout the study, increasing moderately to week 16 but returning to close to baseline values by week 48. The values were considered to represent normal variation.

The total volume of GdE lesions in cohort 1 decreased from 0.305 mL at study day 1 to 0.137 mL at week 16 (a 0.187 mL decrease) and remained reduced at week 48. The lowest value (0.094 mL) was measured at week 36 (figure 3B). In cohort 2, there was greater variability throughout, and the lesion volume at week 48 was comparable to that at baseline.

At week 48, 70.6% (12/17) of participants in cohort 1 were free of GdE lesions, an increase from 52.9% (9/17) at

Figure 2 Flow diagrams



Schematic flow diagrams with participant disposition for (A) study 1 (phase 1b study) and (B) study 2 (phase 2a study), respectively. [a]Completed all 9 doses of ATX-MS-1467 and week-20 visit, [b]attended week-48 visit, [c]entered the baseline control period, [d]visits 8 to 15 (weeks 6–20). AE = adverse event; i.d. = intradermal; s.c. = subcutaneous.

baseline. In cohort 2, the percentages of participants free of GdE lesions were comparable at baseline and week 48. There were no notable changes in the mean number of new or newly enlarging T2 hyperintense lesions.

In study 2, there was a statistically significant decrease in the number of T1 GdE lesions on treatment (average of up to 3 measurements at weeks 12, 16, and 20) compared with baseline (from 7.4 ± 7.62 to 5.0 ± 7.24; $p = 0.0143$) based on a nonparametric analysis. Number and volume of T1 GdE lesions remained reduced from the end of the treatment period to the study end (figure 4). The mean reduction in lesions from baseline ranged from 1.6 to 4.6, and the reduction in lesion volume ranged from 0.579 to 0.225 mL.

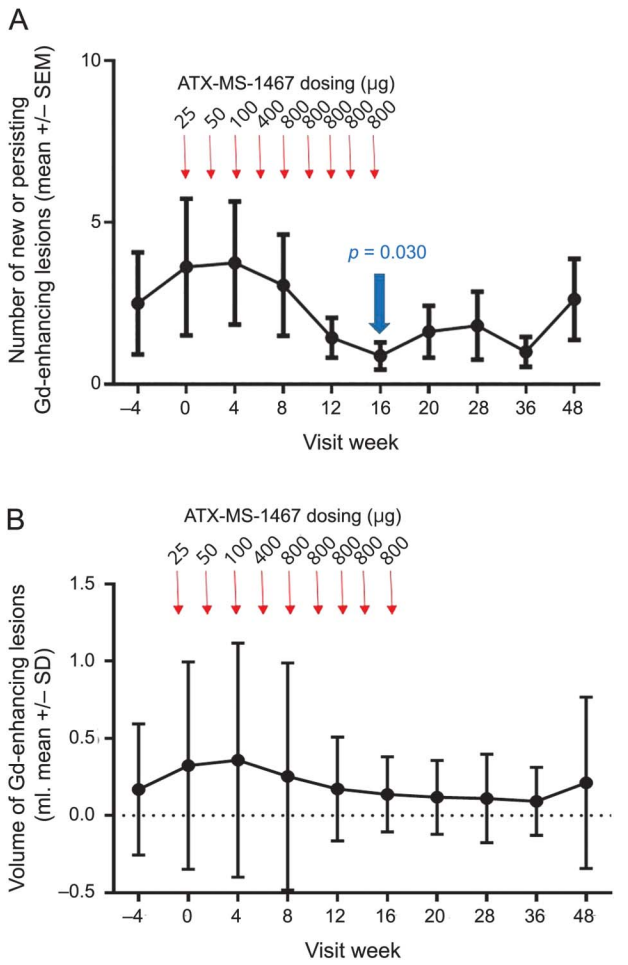
Changes from baseline to the end of treatment in EDSS and MSFC scores were not significant. There were numerical improvements ($p = 0.054$, Wilcoxon matched-pairs signed rank test) during the study in the MSFC score from baseline to the end of the treatment period. This observation drove a post hoc analysis on the MSFC individual score components. The Paced Auditory Serial Addition Test score

Table Demographic characteristics of the study populations at baseline

Variable	Study 1 (n = 43)[a]		Study 2 (n = 19)[b]
	Cohort 1	Cohort 2	
Age, y	33.0 ± 9.5	31.6 ± 9.6	27.1 ± 5.5
Sex, female	17 (81)	13 (59)	15 (79)
Height, cm	164.9 ± 7.9	168.9 ± 8.1	168.8 ± 6.9
Weight, kg	66.2 ± 15.6	67.8 ± 12.8	65.49 ± 16.7
BMI, kg/m^2	24.24 ± 4.9	23.70 ± 3.6	22.78 ± 4.4
EDSS score	2.52 ± 0.9	2.05 ± 0.8	2.32 ± 0.8
MSFC score	NA	NA	0.289 ± 0.52
No. of T1 GdE lesions[c]	3.4 ± 8.2	2.3 ± 5.5	7.4 ± 7.6
Volume of T1 GdE lesions, mL[c]	0.305 ± 0.61	0.189 ± 0.43	0.838 ± 1.02
MS relapses in previous 24 mo			
1–2	18 (86)	22 (100)	17 (90)
3–4	3 (14)	0	2 (10)
ARR	0.58–1.11[d]		
Time since last MS relapse, mo	NA	NA	4.2 ± 3.3

Abbreviations: ARR = annualized relapse rate; BMI = body mass index; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhanced; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; NA = not assessed.
Data represent either mean ± SD or n (%).
[a] Intention-to-treat population.
[b] Safety population.
[c] MRI population; n = 37.
[d] ARR was estimated from the numbers of recorded relapses in the previous 24 months. The lowest value in the range assumes that all patients had 1 or 3 relapses, respectively; the high range assumes 2 or 4 relapses.

Figure 3 Efficacy results in study 1



Number (A) and volume (B) of new or persisting gadolinium (Gd)-enhancing T1 lesions over time in the study 1 cohort 1 per-protocol population (n = 16). Values are mean ± SEM (A) and mean ± SD (B) respectively.

improved significantly ($p = 0.01$) from week 0 to the end of the treatment period.

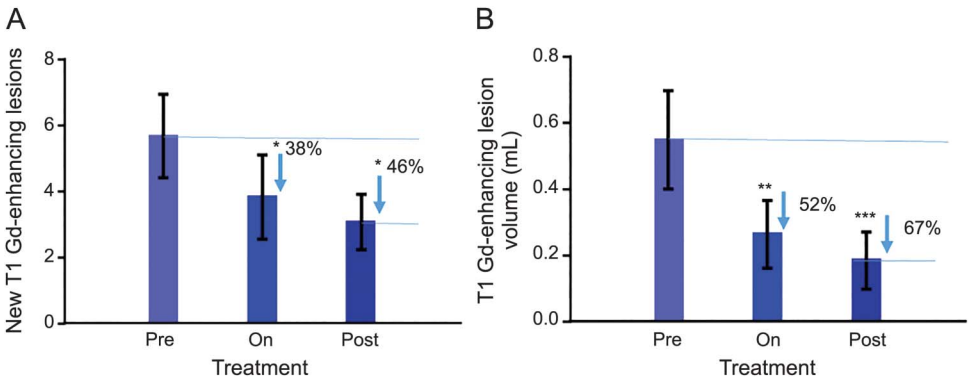
During study treatment, 3 participants (15.8%) experienced single relapses (on days 50, 59, and 89, respectively) corresponding to an ARR of 2.60 for these patients (0.41 for the study population). Participants received rescue corticosteroid therapy. A ≥85% treatment effect was maintained between week 20 and study end for 57% of those participants (7) of the study population who showed >60% decrease in new T1 lesions.

Safety and tolerability

In study 1, 33 participants (77%) experienced a TEAE, all of which were mild or moderate. Twenty participants (47%) experienced treatment-related TEAEs, 14 in cohort 1 (67%) and 6 (27%) in cohort 2. The greater number of participants reporting a treatment-related AE in cohort 1 (i.d. administration) was attributable to a higher number of injection-site reactions (for details, see table e-1, links.lww.com/WNL/A245). In both cohorts, all treatment-emergent injection-site reactions were mild. There were no treatment-related early discontinuations. One patient in cohort 1 discontinued the treatment phase because of an AE (allergic reaction) possibly related to the study medication. There were no severe TEAEs, no treatment-related serious AEs, and no AEs that resulted in dose suspension or withdrawal from the study. There were no reports of drug-related MS relapse in either cohort, nor were there any antibody responses to any ATX-MS-1467 peptides. Treatment-emergent MS relapses were experienced by 2 participants in cohort 1 at weeks 14 and 16, respectively. In cohort 2, 1 participant experienced 2 relapses after treatment at 400 μg and at 800 μg (weeks 6 and 8) and 2 subjects after treatment at 800 μg (weeks 8 and 16). This corresponded to a mean total cohort ARR of 0.15. All participants received steroid rescue therapy and recovered. All relapses were mild or moderate and none was assessed as related to treatment.

In study 2, 15 participants (79%) experienced a TEAE. All were mild or moderate. Eleven TEAEs (58%) were identified as treatment-related. The majority were injection-site reactions: erythema in 5 participants (26%), induration, pain, and

Figure 4 Efficacy results in study 2



Number (A) and volume (B) of new or persisting gadolinium (Gd)-enhancing T1 lesions over time in the study 2 per-protocol population (n = 16). Bars and lines represent mean ± SEM. On treatment represents the average of up to 3 measurements taken at weeks 12, 16, and 20. Post treatment represents the average of up to 2 measurements taken at weeks 28 and 36. *p < 0.05; **p < 0.01; ***p < 0.001.

pruritus each in 2 participants (11%), and hemorrhage in 1 participant (5%). Two participants (11%) experienced treatment-related diffuse alopecia. One participant discontinued treatment because of a TEAE of prolonged, moderate diarrhea, which was considered treatment-related.

Discussion

ATX-MS-1467 is being developed as a potential immunotherapy for MS targeting specifically the autoreactive immune system directed against myelin. This strategy differs from most emerging therapies for MS, which use monoclonal antibodies to target and modify different aspects of the immune system.[15,16] Although an appealing concept, no peptide-based antigen-specific immunotherapy has yet been successful in MS. The results presented here, from a phase 1b and a phase 2a study, further support ATX-MS-1467 as a potentially effective and well-tolerated new therapy.

Dosing and titration regimens are important for antigen-specific immunotherapy. To induce effective tolerance with ATX-MS-1467, a reasonably high dose is considered necessary, as 3 of the 4 MBP peptides in this cocktail display low affinity for major histocompatibility complex binding sites.[11] Earlier work has demonstrated the critical role of a dose-escalation protocol in minimizing $CD4^+$ T cell activation and proliferation during the early stages of immunotherapy, to prevent excessive systemic cytokine release and allow safe administration of the required doses.[8] The 2 trials described in the present communication provide further information to guide an optimized escalation and treatment scheme for ATX-MS-1467 in RMS.

In study 1, a slower 8-week titration period was followed by an 8-week, full-dose treatment period. This corresponded to the regimen in the first in-human study with ATX-MS-1467.[11] Study 2 used a shorter 4-week titration period and a longer 16-week, full-dose treatment period. In both trials, treatment was associated with reductions in the number of T1 GdE lesions, a biomarker for inflammatory disease activity.[17,18] In study 2, the median number of new/enlarging T2 lesions decreased after week 12 and remained reduced at subsequent visits. Of note, there were no safety and tolerability concerns associated with any treatment regimen.

In study 1, the reduction in the number of T1 GdE lesions was greater than the reductions in study 2. However, in the latter trial, the longer full-dose treatment period led to a greater persistence of the effect during off-treatment follow-up. Taken together, these effects on new GdE lesions are comparable to those reported for other MS therapies at similar stages of development.[15]

Although results cannot be directly compared between 2 separate trials, they clearly show that the rate of dose escalation can have a significant effect on efficacy (whereby a longer dose escalation appears to be more favorable). This finding is supported by preclinical data.[8] In addition, longer treatment with the highest dose appears to offer a longer-lasting effect post treatment.

The difference in outcomes between the 2 cohorts in study 1 is consistent with the i.d. route of administration being optimal for immunotherapy with peptides. It does not exclude the efficacy of the s.c. route, as cohort 2 had fewer GdE lesions at baseline and limited scope for improvement. The consistently low disease activity throughout the course of treatment in cohort 2 may be attributable to a protective effect of ATX-MS-1467, but such conclusions are speculative.

Both studies have limitations, particularly the lack of placebo group or randomization, as well as small cohort sizes. In study 1, efficacy was evaluated on secondary endpoints. The Paced Auditory Serial Addition Test results should not be over-interpreted, because the score is susceptible to practice effects, particularly during a short trial.[19] Despite the limitations, these 2 trials, using validated MRI surrogate endpoints[20] and established outcomes for proof-of-concept and phase 2 efficacy trials in RMS,[21] support the use of a relatively slow ATX-

MS-1467 titration procedure combined with a longer full-dose treatment period to achieve effective reduction in T1 GdE lesions during treatment and a sustained effect post treatment. A further phase 2b trial of ATX-MS-1467 in a larger study population is warranted to confirm these findings.

Author contributions

K.M. contributed to the design and management of study 1 and design of study 2. D.W. designed ATX-MS-1467 and contributed to the design of study 1 and 2. K.B. contributed to the design and management of study 1. J.C. was chief investigator of study 1. B.S. was an investigator on study 1. P.S. wrote the manuscript. All authors were involved in the review of the manuscript and approved the final version.

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Disclosure

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Effects of ATX-MS-1467 immunotherapy over 16 weeks in relapsing multiple sclerosis

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